CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-350

SUMMARY REVIEW

Summary Review for Regulatory Action

Date	July 27, 2009
From	Mary H. Parks, M.D.
Subject	Division Director Summary Review
NDA/BLA # Supplement #	22-350
Applicant Name	Bristol Myer Squibb
Date of Submission	June 30, 2008
PDUFA Goal Date	July 31, 2009 (including 3-month extension for major amendment)
Proprietary Name / Established (USAN) Name	Onglyza® (saxagliptin)
Dosage Forms / Strength	2.5 and 5.0 tablets
Proposed Indication(s)	As an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus
Action/Recommended Action for NME:	Approval

Material Reviewed/Consulted OND Action Package, including:	**Names of discipline reviewers**
Medical Officer Review	Naomi Lowy, M.D.
Statistical Review	Roswitha Kelly, M.S. (CMC Stats Review) Karl Lin, Ph.D. (Carci Stats Review) Joy Mele, M.S. Todd Sahlroot, Ph.D. Atair Rahman, Ph.D. (carci Stats Review) Thomas Permutt, Ph.D. Yi Tsong, Ph.D. (CMC Stats Review)
Pharmacology Toxicology Review	Fred Alavi, Ph.D. Todd Bourcier, Ph.D. Paul Brown, Ph.D.
CMC Review/OBP Review	Ali Al-Hakim, Ph.D. Shamista Chatterjee, Ph.D. Blair Fraser, Ph.D. John Hill, Ph.D. Christine Moore, Ph.D. Prafull Shiromani, Ph.D. Su Tran, Ph.D.
Microbiology Review	NA
Clinical Pharmacology Review	Sally Choe, Ph.D. Justin C. Earp, Ph.D. Wei Qiu, Ph.D.

	Christoffer Tornoe, Ph.D. Jaya Vaidyanathan, Ph.D. Immo Zdrojewski, Ph.D.
DDMAC	Robert Dean, M.B.A Kendra Jones, B.S. Sam Skariah, Pharm.D. Sangeeta Vaswani, Pharm D.
DSI	Susan Leibenhaut, M.D. Constance Lewin, M.D., M.P.H.
CDTL Review	Hylton Joffe, M.D., M.M.Sc.
OSE/DMETS	Kristina Arnwine, Pharm.D. Anne Crandall, Pharm.D. Melina Griffis, R.Ph. Carol Holquist, R.Ph. Denise Toyer, Pharm. D.
OSE/DSRCS	Jessica Diaz, RN, BSN Jodi Duckhorn, M.A.
Other	Lina Aljuburi, Pharm. D. Laurie Burke, (SEALD) Jeanne Delasko, RN, MS (SEALD) Abby Jacobs, Ph.D. (Executive CAC) David Jacobson-Kram, Ph.D. (Executive CAC) Barry Rosloff, Ph.D. (Executive CAC)

OND=Office of New Drugs
DDMAC=Division of Drug Marketing, Advertising and Communication
OSE= Office of Surveillance and Epidemiology
DMETS=Division of Medication Errors and Technical Support
DSI=Division of Scientific Investigations
DDRE= Division of Drug Risk Evaluation
DSRCS=Division of Surveillance, Research, and Communication Support
CDTL=Cross-Discipline Team Leader

Division Director Review

1. Introduction

Saxagliptin is a dipeptidyl peptidase-4 enzyme inhibitor (DPP4-inhibitor) developed for the management of hyperglycemia in patients with type 2 diabetes mellitus (T2DM). This is a relatively new class of anti-diabetic therapy whose mechanism of action targets the impaired release and availability of the incretin hormone, glucagon-like peptide-1 (GLP-1) in patients with type 2 diabetes. GLP-1 and another incretin hormone, glucose-dependent insulinotropic polypeptide (GIP), are released from the gastrointestinal tract in response to meals to further stimulate insulin release. Because GLP-1 is rapidly degraded by the serine protease, dipeptidyl peptidase 4, an inhibitor of this enzyme will prolong the half-life of this incretin hormone allowing for a more sustained effect on glucose control.

Unlike other anti-diabetic therapies, which control hyperglycemia through stimulation of insulin release from the pancreas (e.g. sulfonylureas or glinides), incretin-based therapies control hyperglycemia through a glucose-dependent manner thereby mitigating the risk of hypoglycemia. GLP-1 receptor agonists are another class of incretin-based therapies. These agents are manufactured to avoid susceptibility to enzyme degradation while maintaining sufficient cross-reactivity with the GLP-1 receptor to impart similar effects on glucose control as the native hormone.

Currently, Januvia (sitagliptin) is the only marketed DPP4-inhibitor in the United States.

b(4)

2. Background

Over the past two to three years, concerns regarding the cardiovascular safety profile of certain anti-diabetics have resulted in much debate within the scientific and regulatory community on the adequacy of the development programs for anti-diabetic therapies to ensure that these drugs do not contribute to excess cardiovascular mortality and morbidity in a patient population that is already at 2- to 4-fold risk of dying from heart disease.

On July 1 and 2, 2008, the FDA convened a public advisory committee meeting to discuss the role of CV assessment in the pre- and postmarket settings. The pivotal question raised to the panel members was:

It should be assumed that an anti-diabetic therapy with a concerning CV safety signal during Phase 2/3 development will be required to conduct a long-term cardiovascular trial. For those drugs or biologics without such a signal, should there be a requirement to conduct a long-term cardiovascular trial or to provide other equivalent evidence to rule out an unacceptable cardiovascular risk. (vote yes/no requested).

The outcome was 14 "yes" and 2 "no" votes.

Following this advisory committee meeting, the FDA issued a Final Guidance to Industry in December 2008 titled, *Diabetes Mellitus – Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes.* With its release, the FDA also publicly announced that the recommendations in this guidance will be applied to all ongoing diabetes development programs and marketing applications pending before the agency. In order to gain approval, applicants must compare the incidence of important cardiovascular events occurring with the investigational agent to the incidence of the same types of events occurring with the control group to show that the upper bound of the two-sided 95 percent confidence interval for the estimated risk ratio is less than 1.8.

At the time of its issuance, the FDA had three NDAs under review: ( ) saxagliptin (Onglyza), and liraglutide (Victoza). Saxagliptin and liraglutide were each presented at a public advisory committee meeting on April 1 and 2, 2009, respectively. b(4)

( ) Because none of these NDAs were conducted with knowledge of these new recommendations, the review division applied a uniform approach to assessing risk for these NDAs. This approach is clearly described by the clinical and statistical reviewers in their finalized review of this NDA and also in the advisory committee briefing materials. This memo will summarize how this applicant has met the new regulatory requirements for establishing sufficient cardiovascular safety for approval under Section 8.0.

The advisory committee meeting for saxagliptin focused only on the cardiovascular risk assessment. An in-depth review of efficacy was not presented by FDA at that time; however, the applicant did provide data supporting a conclusion that therapy with saxagliptin results in significant reductions in HbA1c, as both monotherapy and in combination with several other anti-diabetic agents. The finalized statistical review by Ms. Mele provides greater detail of the efficacy findings, including variables which may have influenced efficacy and flaws in the study designs which must be considered in the interpretation of efficacy. Section 7.0 of my memo will present the highlights of her findings.

In addition to cardiovascular safety, signals identified in the nonclinical program that have also directed the clinical safety review are summarized in this memo. Some of these safety signals appear to be a class effect observed in several clinical development programs (e.g., hypersensitivity reactions) or in the nonclinical toxicology programs (e.g., cutaneous lesions). Spontaneous postmarketing adverse event reports of pancreatitis for other incretin-based therapies have also necessitated a careful evaluation in this NDA.

3. CMC/Device

Saxagliptin tablets are available as 2.5 or 5 mg film-coated tablets. There are no outstanding CMC issues. Manufacturing site inspections were acceptable. Stability testing supports an expiry of 36 months for the 2.5 mg tablets supplied in 30- and 90-count bottles containing dessicant. The 5 mg tablets supplied in 30-, 90-, and 500-count bottles containing dessicant or when stored in aluminum/aluminum blisters also have an expiry of 36 months. Recommended storage conditions for all presentations is 25^0C (77°F) with excursions permitted to 15°-30°C (59°-86°F).

4. Nonclinical Pharmacology/Toxicology

The pharmacology/toxicology reviewers have recommended approval of this NDA. In Dr. Alavi's review he stated the following:

"Subchronic and chronic toxicology studies in mice, rats, dogs, and monkeys identified several areas of potential human concern: a) brain lesions in male rats, b) cutaneous lesions in cynomolgus monkeys and footpad cracks in dogs, c) malformations in embryofetal development in rats with saxagliptin/metformin combination, d) saxagliptin-related decreased in lymphocytes and platelets and immune system."

For each of these areas of concern, both Drs. Alavi and Bourcier have provided a thorough scientific review, including relevance of findings to humans. I concur with their conclusion that these concerns do not preclude the approval of this NDA but labeling will reflect these findings and two post-marketing required studies will be necessary under FDAAA to address teratogenicity concerns with the combined use of saxagliptin and metformin. In this section I will only highlight the first 3 issues. The clinical setting was deemed to be more appropriate for assessing the effects of saxagliptin on the hematopoietic and immune system.

4.1 Brain Lesions in Male Rats

Brain lesions (predominantly in the corpus callosum) were noted only in male Sprague-Dawley rats and at high doses (355x the maximum therapeutic dose of saxagliptin, based on AUC). From a series of mechanistic studies it was concluded that these lesions were the result of a gender and species-specific metabolism of saxagliptin. Rats express CYP2C11, an androgen-regulated liver enzyme which causes the release of cyanide from saxagliptin resulting in the histopathological findings resembling what has been described in the literature for cyanide poisoning. Support for the conclusion that this toxicity is specific to the expression of this androgen-regulated liver enzyme was the absence of such findings when the study was conducted in castrated rats or in rats receiving cimetidine, a CYP2C11 inhibitor.

In humans, saxagliptin is predominantly metabolized in the liver by CYP3A4/5. Incubation studies of saxagliptin in human liver microsomes (CYP2C8, 2C18, and 2C19) did reveal small amounts of cyanide formation that were below the lower limits of quantitation. Given the absence of CYP2C11 in humans and no notable detection of cyanide in HLM studies, the

pharmtox reviewers have concluded that the brain lesions noted in male rats at very high multiples of drug exposure have no clinical relevance.

4.2 Cutaneous Lesions in Monkeys and Dogs

Some other DPP4-inhibitors in development have been associated with peripheral skin lesions, cutaneous sores, peripheral edema, and severe swelling associated with CK and LFT elevations. As a result, all manufacturers are required to conduct a 13-week monkey study to evaluate the potential for causing the peripheral lesions which may be due to non-selectivity of the compound for other dipeptidyl peptidases. Minimal and reversible non-necrotizing cutaneous lesions were observed in several animals treated with saxagliptin at exposures ≥ 20x the clinical dose. Severe necrotizing lesions were observed only at 60x the clinical dose. In a 12-month dog study, minimal erosive lesions were noted on the paws but this was at exposures ≥ 35x the clinical dose.

Given the high multiples of clinical exposures before any of these cutaneous lesions were noted, these findings are not considered to be of sufficient clinical risk.

4.3 Embryofetal Malformations

Co-administration of saxagliptin and metformin was associated with a rare and serious neural tube defect (craniorachischisis) in two fetuses from a single dam in a rat reproductive toxicology study. This was not an expected finding as saxagliptin alone was not associated with any malformations at doses exceeding 1500x clinical exposure. In addition, such a malformation has not been observed in the nonclinical studies submitted for approval of metformin. The applicant provided literature to suggest this finding was related to metformin and its effect on folate metabolism; however, the applicant did not include a metformin-only arm to adequately assess this hypothesis. Given that most anti-diabetic drugs are co-administered with metformin, the pharmtox reviewers are recommending a more appropriate embryofetal toxicology study be conducted in both rats and rabbits involving a metformin-only, saxagliptin-only, and a combination arm as post-marketing required studies under FDAAA. Labeling will include the findings from the current study.

Several points which require discussion is the timing of these two embyrofetal toxicology studies. The pharmtox and clinical review disciplines did not feel that these two studies were necessary pre-approval. It was felt that while the neural tube defect finding is a serious finding, it occurred in only 2 fetuses from the same litter. Given the absence of teratogenicity findings for both saxagliptin and metformin monotherapies, there is a strong possibility that this was a spurious finding for which labeling could provide adequate data to inform prescribers on a theoretical risk such that a decision can be made regarding co-prescribing with metformin in women of childbearing potential.

There were discussions regarding whether the label should include a contraindication against the co-administration of saxagliptin and metformin. FDA's Reproductive and Development Toxicological Subcommittee and the Director and Associated Director of pharmacology/toxicology did not deem this to be necessary. I concur with this

recommendation. The repeat reproductive toxicology studies will be completed by ( ) and submitted to the FDA by April 30, 20( ) Upon review of these data, labeling will be updated if warranted. b(4)

5. Clinical Pharmacology/Biopharmaceutics

Clinical pharmacology reviewers recommend approval of this NDA. As there are no internal disagreements regarding any recommendations made by this discipline, my memo will only highlight relevant clinical findings, particularly those requiring special emphasis in labeling with respect to dosing instructions or special monitoring.

Saxagliptin is metabolized predominantly by CYP3A4/5 to BMS-510849 which is present in human plasma at 2 to 7-fold higher levels than the parent drug. Although BMS-510849 is an active metabolite, it is less potent than the parent drug but has greater selectivity for DPP4 over DPP8 than the parent drug. These attributes of the metabolite are reassuring as there is less concern for off-target toxicity with respect to cutaneous lesions. Animal toxicology studies have also included assessments of this metabolite and other minor metabolites.

The kidney is the major route of elimination of the parent compound and the metabolite. As such, renal function affects the exposure of saxagliptin and its metabolite. Patients with severe renal impairment had a 2.1-fold increase in saxagliptin exposure compared to control subjects and both severe renal impairment and hemodialysis were associated with an approximate 4-fold increased in BMS-510849. Patients with moderate renal impairment had a less pronounced increased in exposure to saxagliptin (40%) and its metabolite (~3-fold); however, this was felt to be clinically relevant such that the lowest proposed dose of 2.5 mg is recommended for patients with moderate and severe renal impairment and with ESRD. The applicant is currently conducting a dedicated safety trial in patients with renal impairment.

Several drug-drug interaction studies were performed and discussed in detail in Dr. Vaidyanathan's review. Interestingly, two DDI studies were performed with the strong CYP3A4/5 inhibitor, ketoconazole. The first one utilized a single high dose of saxagliptin 100 mg with ketoconazole 200 mg q12 given for 6 days. This study resulted in a 2.5-fold increase in saxagliptin exposure and a 1.62-fold increase in Cmax. Not surprisingly, the metabolite exposure decreased. Because 14 out of 15 patients experienced a decline in lymphocyte counts on Day 10 following the co-administration of saxagliptin and ketoconazole, a second PK study was conducted which used saxagliptin 20 mg which now resulted in a 3.8-fold increase in saxagliptin exposures. This study also showed a 30.6% decrease in absolute lymphocyte count which returned to baseline 72 hrs after study drug discontinuation. Since a near 4-fold exposure increase was observed with a strong CYP3A4/5 inhibitor that results in drug levels not evaluated in the Phase 3 program, I concur with clinical pharmacology's recommendation to limit dosing of saxagliptin to 2.5 mg in patients receiving concurrent strong CYP3A4/5 inhibitors.

Several DDP4 inhibitors in development have selected doses based on the drug's ability at maintaining DPP4 inhibitory activity > 80% after 24 hours. For the two doses selected for

marketing, saxagliptin 2.5 and 5 mg administered for 14 days in patients with T2DM resulted in DPP4 inhibitory activity of 37% and 65%, respectively, after 24 hours. Despite this, the degree of HbA1c reduction in the pivotal Phase 3 trials appears similar between saxagliptin and other DPP4 inhibitors (e.g., sitagliptin) achieving a greater degree of DPP4 inhibitory activity. This would suggest that DPP4 inhibitory activity is not a reliable predictor of efficacy, particularly in Phase 2 dose-selection studies.

Ms. Mele's statistical review observed a statistically significant interaction between Asian race and efficacy raising the possibility of PK differences and possibly safety in Asians. From Figure 25 in Dr. Vaidyanathan's review there was no difference in the clearance of saxagliptin between Asians and other races evaluated. The clearance of the metabolite was slightly elevated compared to other races. None of these changes would explain the significant interaction between Asian ethnicity and efficacy.

6. Clinical Microbiology

Not applicable.

7. Clinical/Statistical-Efficacy

Similar to other clinical development programs for anti-diabetic therapies, the primary efficacy endpoint for all pivotal Phase 3 trials was HbA1c, a validated surrogate for the reduction of microvascular complications associated with both type 1 and type 2 diabetes. Secondary endpoints which further evaluate the effect of drug on glycemic parameters included fasting plasma glucose (FPG), proportion of patients reaching a HbA1c < 7%, and AUC from 0-180 minutes for post-prandial glucose (PPG) in response to an oral glucose tolerance test (OGTT).

This NDA included clinical efficacy and safety from 8 Phase 2 and 3 trials. For the purpose of this section, my memo will primarily focus on the 6 pivotal Phase 3 trials summarized in Table 7.1 below. Another study not discussed at length in my memo is Study CV181008 (008). This was a 12-wk, Phase 2 dose-ranging study which evaluated saxagliptin 2.5 mg, 5 mg, 10 mg, 20 mg, 40 mg, and 100 mg which found statistically significant differences in mean percent change form Baseline in HbA1c relative to placebo but no dose response.

Table 7.1 Summary of Pivotal Phase 3 Trials

Study Number	Treatment Groups (number randomized)	Patient Population	Study Duration (primary efficacy assessment duration listed first)
Monotherapy Trials			
CV181011	Saxa 2.5 (n=102) Saxa 5 (n=107) Saxa 10 (n=98) Pbo (n=96)	Drug-naïve Mean Baseline HbA1c (7.8-8.0)	24 weeks 18 months+ LT ongoing
CV181038	Saxa 2.5 qAM (n=n=74) Saxa 2.5 titrate to 5 qAM (n=71) Saxa 5 qAM (n=74) Saxa 5 qPM (n=72)	Drug-naïve Mean Baseline HbA1c (7.8-8.0)	24 weeks 12 months+ LT ongoing

	Pbo (n=74)		
Add-on Trials			
CV181013	TZD+Saxa 2.5 (n=195) TZD+Saxa 5 (n=186) TZD+Pbo (n=184)	TZD failures Mean Baseline HbA1c = 8.3	24 weeks 12 months+ LT ongoing
CV181014	Met+Saxa 2.5 (n=192) Met+Saxa 5 (n=191) Met+Saxa 10 (n=181) Met+Pbo (n=179)	Metformin failures Mean Baseline HbA1c = 8.0	24 weeks 12 months+ LT ongoing
CV181040	Gly7.5+Saxa 2.5 (n=248) Gly10+Saxa 5 (n=253) Gly10+Pbo (n=267)	SU failures Mean Baseline HbA1c = 8.4	24 weeks 12 months+ LT ongoing
Combination Trials			
CV181039	Saxa 5+Met (n=320) Saxa 10+Met (n=323) Saxa 10 (n=335) Met (n=328)	Drug-naïve Mean Baseline HbA1c (9.4-9.6)	24 weeks 12 months+ LT ongoing

The primary efficacy analysis for all of these studies was at Week 24 and the study designs were similar in that they were all randomized and double-blinded trials and continuation into an extension period was not voluntary and included patients who required rescue therapy for glycemic control. The double-blind, randomized treatments were continued into the extension period, a characteristic of these studies which enable a better evaluation of safety (See Section 8.0).

As in other trials of anti-diabetic therapies, there are rescue criteria incorporated into the study designs to address progressive worsening of glycemic control, particularly for studies of < 6 months duration. While this has become standard practice due to the notion that it is unethical to ignore worsening glycemic control in a clinical investigation, the addition of other anti-diabetic therapies or the discontinuation of study participants (not done in the saxagliptin program) presents challenges to the interpretation of drug efficacy. This is extensively discussed in Ms. Mele's review for each pivotal trial studied and separately in Section 3.1.4 of her review. The criteria for initiating glycemic rescue therapy can be found in Tables 5.4 and 5.5 of Dr. Lowy's review. Noteworthy is that the time point for determining whether additional therapy is necessary is before Week 26, the time point for the primary efficacy analysis. Hence, there will be some proportion of patients at Week 26 who will have data from their last measured HbA1c prior to rescue therapy contributing to the overall efficacy analysis. Across all trials, poorer control of diabetes at Baseline (HbA1c, FPG) and a higher BMI predicted a higher incidence of rescue therapy.

Across the monotherapy and add-on pivotal Phase 3 trials, the different doses of saxagliptin studied achieved statistically greater reduction in HbA1c from Baseline relative to placebo. The difference in mean adjusted HbA1c change ranged from -0.4 to -0.8%. There was no greater HbA1c reduction observed with saxagliptin 10 mg daily dosing. The applicant is proposing to market both the 2.5 and 5 mg doses with the 5 mg dose to be used in the general

diabetic population while the 2.5 mg dose is reserved for patients with renal insufficiency. Although there is little evidence of a dose response between the 2.5 and 5 mg doses, Ms. Mele wrote a separate memo dated June 25, 2009 which specifically evaluated the 71 patients in Study 38 who had their dose titrated from saxagliptin 2.5 mg to 5.0 mg. Her review suggests that for some patients initiated on therapy at the 2.5 mg dose and who do not have an adequate glycemic response, upward titration to 5 mg may provide additional reductions in HbA1c. These data would support having both doses available but the applicant should not be allowed to promote the 5 mg dose as the recommended start dose for the majority of patients.

In Study 39 which evaluated the use of saxagliptin+metformin as initial therapy compared to the individual components, the use of the two agents in combination provided greater reductions than saxagliptin 10 mg or metformin monotherapy. Ms. Mele noted that the absence of a saxagliptin 5 mg monotherapy would require a comparison of the saxagliptin 5 mg + metformin treatment group to saxagliptin 10 mg monotherapy. Given that all other Phase 3 trials have shown similar efficacy between saxagliptin 5 and 10 mg, I believe the results from this comparison would yield a similar finding if the applicant had included a saxagliptin 5 mg, especially since the saxagliptin 5 mg + metformin efficacy is superior to saxagliptin 10 mg monotherapy (LS Mean 0.84; $p<0.0001$). A noteworthy point made by Ms. Mele is that there was a significantly higher percentage of patients requiring rescue therapy in the saxagliptin 10 mg treatment arm (20%) than observed in the saxagliptin arms in other trials despite the enrollment of treatment-naïve patients. This might reflect the higher Baseline HbA1c in this trial. Regardless, it would suggest that saxagliptin 2.5 or 5 mg monotherapy would not be a reasonable initial therapy for patients with poor glycemic control.

8. Safety

Drs. Lowy and Joffe have provided a detailed assessment on the safety of saxagliptin and have not identified a safety issue that will preclude the approval of this NDA. However, there are safety issues which have contributed to the postmarketing requirements outlined in the action letter which merit discussion in my memo.

8.1 Cardiovascular Safety

As discussed under the Background section of this memo, this applicant was required to show adequate CV safety with saxagliptin based on the recently implemented requirements outlined in the December 2008 FDA Guidance to Industry. The entire clinical development program intended for support of an NDA for saxagliptin was designed and completed prior to the issuance of this Guidance. As a result, prospective adjudication of CV events was not possible for this application. Instead, a method for post-hoc evaluation of CV events collected in this NDA was proposed by FDA for saxagliptin and other NDAs pending before the FDA at the time the guidance was made public. Dr. Lowy's review and the background materials provided for the April 1, 2009 advisory committee meeting have outlined the details of the methodology for selecting CV events for a risk assessment. Table 8.1 summarizes the Preferred Terms which would be selected for analyses of "Broad MACE SMQ" and the more specific "FDA Custom MACE".

Table 8.1 Definitions for Different MACE analyses

	"Broad MACE SMQ"	"FDA Custom MACE"
Myocardial Infarction Terms		
Acute coronary syndrome	x	
Acute myocardial infarction	x	X
Blood creatine phosphokinase abnormal	x	
Blood creatine phosphokinase increased	x	
Blood creatine phosphokinase MB abnormal	x	
Blood creatine phosphokinase MB increased	x	
Cardiac arrest		
Cardiac enzymes increased	x	
Circulatory collapse		
Coronary artery embolism	x	
Coronary artery occlusion	x	
Coronary artery reocclusion	x	
Coronary artery thrombosis	x	X
Coronary bypass thrombosis	x	
Electrocardiogram Q wave abnormal	x	
Electrocardiogram ST segment abnormal	x	
Electrocardiogram ST segment elevation	x	
Electrocardiogram ST-T segment elevation	x	
Infarction	x	
Myocardial infarction	x	X
Myocardial reperfusion injury	x	
Papillary muscle infarction	x	X
Postinfarction angina	x	
Postprocedural myocardial infarction	x	X
Scan myocardial perfusion abnormal	x	
Silent myocardial infarction	x	X
Troponin I increased	x	
Troponin increased	x	
Troponin T increased	x	
Vascular graft occlusion	x	
Stroke Terms		
Agnosia	x	
Amaurosis fugax	x	
Angiogram cerebral abnormal	x	
Aphasia	x	
Balint's syndrome	x	
Basal ganglia hemorrhage	x	
Basilar artery occlusion	x	
Basilar artery stenosis	x	
Basilar artery thrombosis	x	X
Brain stem hemorrhage	x	
Brain stem infarction	x	X
Brain stem ischemia	x	
Brain stem stroke	x	X
Brain stem thrombosis	x	X
Capsular warning syndrome	x	
Carotid aneurysm rupture	x	

	"Broad MACE SMQ"	"FDA Custom MACE"
Carotid arterial embolus	x	X
Carotid arteriosclerosis	x	
Carotid artery aneurysm	x	
Carotid artery bypass	x	
Carotid artery disease	x	
Carotid artery dissection	x	
Carotid artery insufficiency	x	
Carotid artery occlusion	x	
Carotid artery stenosis	x	
Carotid artery stent insertion	x	
Carotid artery thrombosis	x	X
Carotid endarterectomy	x	
Central pain syndrome	x	
Cerebellar artery occlusion	x	
Cerebellar artery thrombosis	x	
Cerebellar embolism	x	
Cerebellar hematoma	x	
Cerebellar hemorrhage	x	
Cerebellar infarction	x	X
Cerebellar ischemia	x	
Cerebral aneurysm ruptured syphilitic	x	
Cerebral arteriosclerosis	x	
Cerebral arteriovenous malformation hemorrhagic	x	
Cerebral artery embolism	x	X
Cerebral artery occlusion	x	
Cerebral artery stenosis	x	
Cerebral artery thrombosis	x	X
Cerebral hematoma	x	
Cerebral hemorrhage	x	
Cerebral hemorrhage fetal	x	
Cerebral hemorrhage neonatal	x	
Cerebral infarction	x	X
Cerebral infarction fetal	x	
Cerebral ischemia	x	
Cerebral thrombosis	x	X
Cerebral vasoconstriction	x	
Cerebral venous thrombosis	x	
Cerebrovascular accident	x	X
Cerebrovascular accident prophylaxis	x	
Cerebrovascular disorder	x	
Cerebrovascular insufficiency	x	
Cerebrovascular spasm	x	
Cerebrovascular stenosis	x	
Charcot-Bouchard microaneurysms	x	
Cranial nerve palsies multiple		
Diplegia	x	
Dysarthria	x	
Embolic cerebral infarction	x	X
Embolic stroke	x	X
Facial palsy		
Hematomyelia	x	
Hemiparesis	x	

	"Broad MACE SMQ"	"FDA Custom MACE"
Hemiplegia	x	
Hemorrhage intracranial	x	
Hemorrhagic cerebral infarction	x	X
Hemorrhagic stroke	x	X
Hemorrhagic transformation stroke	x	X
Intracerebral aneurysm operation	x	
Intracerebral hematoma evacuation	x	
Intracranial aneurysm	x	
Intracranial hematoma	x	
Intraventricular hemorrhage	x	
Intraventricular hemorrhage neonatal	x	
Ischemic cerebral infarction	x	X
Ischemic stroke	x	X
Lacunar infarction	x	X
Lateral medullary syndrome	x	X
Meningorrhagia	x	
Millard-Gubler syndrome	x	
Monoparesis	x	
Monoplegia	x	
Moyamoya disease	x	X
Paralysis	x	
Paralysis flaccid	x	
Paraparesis	x	
Paraplegia	x	
Paresis	x	
Postprocedural stroke	x	X
Precerebral artery occlusion	x	
Putamen hemorrhage	x	
Quadriparesis	x	
Quadriplegia	x	
Red blood cells cerebrospinal fluid positive	x	
Reversible ischemic neurologic deficit	x	
Ruptured cerebral aneurysm	x	
Spastic paralysis	x	
Spastic paraplegia	x	
Spinal artery embolism	x	
Spinal cord hemorrhage	x	
Spinal epidural hemorrhage	x	
Spinal hematoma	x	
Stroke in evolution	x	X
Subarachnoid hemorrhage	x	
Subarachnoid hemorrhage neonatal	x	
Subdural hemorrhage	x	
Subdural hemorrhage neonatal	x	
Thalamic infarction	x	X
Thalamus hemorrhage	x	
Thrombotic cerebral infarction	x	X
Thrombotic stroke	x	X
Transient ischemic attack	x	
Vascular encephalopathy	x	
Vertebral artery occlusion	x	
Vertebral artery stenosis	x	

	"Broad MACE SMQ"	"FDA Custom MACE"
Vertebral artery thrombosis	x	
Vertebrobasilar insufficiency	x	
Visual midline shift syndrome	x	
Wallenberg syndrome	x	X

The following table is obtained directly from Ms. Mele's review and was also presented at the April 1, 2009 advisory committee meeting.

Table 3.2.1 Summary of MACE Results*

	Saxagliptin (n=3356)	Comparator (n=1251)	Common Odds Ratio Stratified on Study (95% CI)
Custom MACE			
ST	4 (0.1%)	7 (0.6%)	**0.21 (0.04, 0.8)**
ST+LT	23 (0.7%)	17 (1.3%)	**0.52 (0.3, 1.0)**
SMQ MACE			
ST	58 (1.8%)	25 (2.0%)	0.90 (0.6, 1.5)
ST+LT	100 (3.1%)	41 (3.2%)	0.96 (0.7, 1.4)

*The ST+LT database for the FDA analyses is the 120-day safety update database

From these results the majority of the AC members concluded that saxagliptin has satisfied the requirements for approval with respect to excluding the 1.8 goal post. While one can also argue that a more definitive assessment of CV risk which excludes the 1.3 upper bound of the 95% CI has also been satisfied by the applicant, the AC members unanimously voted for additional cardiovascular safety assessment in the post-marketing setting. In light of the low CV event rate (reflecting a low risk population studied thus far) and the absence of prospective adjudication of events, the FDA will require a postmarketing trial to provide a more definitive CV risk assessment for saxagliptin.

8.2 Hypersensitivity Reactions

Shortly after the approval of Januvia (sitagliptin), spontaneous postmarketing reports of allergic and hypersensitivity reactions were received resulting in labeling changes to the Warnings and Precautions section as follows:

> *There have been postmarketing reports of serious allergic and hypersensitivity reactions in patients treated with Januvia such as anaphylaxis, angioedema, and exfoliative skin conditions including Stevens-Johnson syndrome.*

Other DPP4-inhibitors have also had clinical and nonclinical findings of hypersensitivity-like reactions. Alogliptin had hypersensitivity-like reactions in its chronic dog studies and a higher rate of similarly-coded reactions was observed with alogliptin in the clinical trials. Noteworthy were two cases of angioedema including one which had a positive rechallenge and dechallenge.

In this NDA, there was an imbalance in hypersensitivity reactions not favoring saxagliptin (2.4%; 50 cases vs 0.6%; 5 cases) when evaluating the pooled Phase 3 monotherapy and add-

on trials, including the 120-day safety update. From Table 13 in Dr. Joffe's review, the majority of these hypersensitivity reactions was coded only as hypersensitivity (saxagliptin n=18, placebo n=0) followed by urticaria (saxagliptin n=16, placebo n= 2). Angioedema was reported in one saxagliptin-treated patient. Drs. Joffe and Lowy have provided selected narratives of some of these cases and recent information request to the firm to provide narrative for all 18 cases of hypersensitivity in the saxagliptin arm revealed no signs or symptoms suggestive of a severe anaphylaxis-like reaction. Of note, no patients required discontinuation of study drug.

The labeling should include information about the imbalance in hypersensitivity-like reactions and postmarketing reports should be specifically monitored for such events.

8.3 Infections

Due to nonclinical findings of decreased lymphocyte counts and a decrease in absolute lymphocyte counts in two clinical pharmacology studies, a careful assessment of rates of infection was undertaken in the review of this NDA. There was not a marked imbalance in infections, including unusual/atypical infections between saxagliptin and comparators. There was a higher incidence of lymphocytopenia ($\leq 0.75 \times 10^3$ c/mcL) in the combine saxagliptin group (1.4%) compared to controls (0.7%) and as summarized in Dr. Joffe's memo, other analyses continued to show a slightly higher incidence of lymphocytopenia in saxagliptin-treated patients. Although this NDA did not identify any serious clinical consequence of this laboratory finding, labeling should inform prescribers of the observed effect on lymphocyte counts with recommended monitoring when clinically appropriate.

8.4 Pancreatitis

In February 2009, Merck submitted a CBE for Januvia to include acute pancreatitis as an event reported in the postmarketing setting. The Office of Surveillance and Epidemiology has also been consulted on evaluating the reporting rates of pancreatitis between Januvia and Byetta, a GLP-1 receptor agonist. Both of these drugs have also had post-marketing reports of hemorrhagic necrotizing pancreatitis.

In this NDA, there was an identical rate of pancreatitis reported between saxagliptin (0.2%) and the comparators (0.2%). None of these cases was necrotizing or hemorrhagic. At this time there is no evidence of an imbalance for risk of pancreatitis with saxagliptin and there is insufficient evidence to consider class labeling for this adverse event based on experience with Byetta and Januvia. However, the applicant should be required to prospectively assess pancreatitis risk in its long-term CV safety trial and any report of pancreatitis in the postmarketing setting should be submitted as 15-day expedited reports to the FDA.

8.5 Liver Safety

In the pooled Phase 2/3 trials database, including data from the 120-day safety update, the incidence of ALT > 3 and 5xULN was similar between saxagliptin and control; however, in looking at greater elevations (> 10x ULN), all cases (n=4) were in saxagliptin-treated patients. Dr. Joffe has provide narratives for all of these cases; two had confirmed diagnoses of viral hepatitis; the other two patients had resolution of transaminitis with discontinuation of saxagliptin and did not have laboratory findings meeting the strict definition of Hy's Law.

In the 120-day safety update, another case was reported which involved a 60-year old man with ESRD on hemodialysis whose ALT levels rose to 2,375 U/L (60x ULN) on Day 19. Hepatitis testing was reportedly negative and concomitant medications included quinapril and gingko biloba. Study medication was discontinued 5 days after the event was noted and two days later ALT levels had declined to 537 U/L. Bilirubin levels were < 2x ULN. This case prompted request for any additional cases of severe transaminitis since the 120-day safety update. A search of data from June 20, 2008 to July 1, 2008 for any cases with ALT > 10xULN or any Hy's law (ALT > 3xULN and total bilirubin > 2xULN) identified the following 7 additional cases. Six of the cases remain blinded while the 7th case involved a 58 year old woman who received saxagliptin 5 mg qam.

After reviewing the narratives of each of these cases, FDA requested that all remaining cases be unblinded. Of the 6 cases, 2 were in saxagliptin-treated patients, 3 were in glipizide-treated patients, and one patient was receiving placebo. Due to concerns regarding data integrity of these ongoing studies, my memo will not disclose the details of the study (protocol #) or patient ID.

This recently received information is reassuring for several reasons. For all the cases involving saxagliptin, study medication was not discontinued as a result of transaminitis and the abnormalities resolved or were listed as ongoing or unknown. In reviewing these narratives, the case which was listed as ongoing involved a 36-year old man whose Baseline LFTs and bilirubin levels were normal. Serologic screening tests for Hepatits A and B were negative. Throughout the study, ALT and AST values fluctuated, including some values above the ULN but bilirubin levels always remained within the normal limits. About 6 months after initiating study drug, ALT values climbed to > 100 (6-48 IU/L) and progressed to peak at 509 with accompanying AST 531 (10-45 IU/L) about 1 year after study enrollment. Bilirubin was normal at 0.9 (0.2-1.2 g/dL), as were alkaline phophatase and albumin levels. According to the sponsor, the patient's study medication was discontinued around this time because of worsening glycemic control. The last laboratory values showed a decline in transaminases but not yet normalization of values resulting in the case being reported as ongoing. The investigator reported suspected excess alcohol intake. The second saxagliptin case which had an unknown outcome involved a 62-year old female with ESRD on hemodialysis. The patient was hospitalized for poor peripheral circulation of her left leg and liver function tests were reported as normal at that time. During the course of her hospitalization, she experienced an MI and study drug was discontinued. Her hospital course was further complicated by development of gangrene toe requiring "left leg amputation at the knee". It wasn't until 22 days after study drug was discontinued did the patient have an elevated ALT of 981 (6-37 IU/L), AST 124 (10-36 IU/L) but with a normal bilirubin of 0.8 (0.2-1.2 mg/dL). No additional laboratory measures are available at this time.

In conclusion, the finding of severe transaminitis, but not Hy's law, in a 60-year old male patient with ESRD on hemodialysis prompted a closer evaluation of the updated database. These data do not present any more cases implicating saxagliptin as a serious hepatotoxin precluding approval. However, I agree that a more extensive evaluation of hepatic events post-marketing is necessary and should be conducted as required studies under FDAAA.

8.6 Fractures

An imbalance in fractures was noted in this NDA as summarized in the following table obtained directly from Dr. Joffe's CDTL memo.

Table 10. Fractures – phase 3 short-term and long-term periods combined, including rescue (monotherapy, add-on combination trials, and initial combination with metformin trial) (120-day safety update database)

	Saxa 2.5 mg N=882 n (%)	Saxa 5 mg N=1202 n (%)	Saxa 10 mg N=937 n (%)	All Saxa N=3021 n (%)	Comparator N=1127 n (%)
Patients with at least 1 fracture event	**14 (1.6)**	**11 (0.9)**	**10 (1.1)**	**35 (1.2)**	**7 (0.6)**
Patients with a typical osteoporotic fracture	**6 (0.7)**	**4 (0.3)**	**2 (0.2)**	**12 (0.4)**	**1 (0.1)**
Rib fracture	3 (0.3)	2 (0.1)	1 (0.1)	6 (0.2)	0
Spinal compression fracture	0	1 (0.1)	0	1 (<0.1)	0
Hip fracture	1 (0.1)	1 (0.1)	0	2 (0.1)	0
Radius fracture	2 (0.2)	0	1 (0.1)	3 (0.1)	1 (0.1)
Patients with other fractures	**8 (0.9)**	**7 (0.6)**	**8 (0.9)**	**23 (0.8)**	**6 (0.5)**
Facial fracture (excluding nose)	0	1 (0.1)	0	1 (<0.1)	0
wer limb fracture (excluding hip)	5 (0.6)	4 (0.3)[2]	5 (0.5)	14 (0.5)	4 (0.4)
Upper limb fracture (excluding radius)	4 (0.5)[1]	2 (0.1)	3 (0.3)	9 (0.3)	3 (0.3)[3]

[1]One patient had two events of upper limb fracture
[2]A report of stress fracture of the tibia occurring in a saxagliptin 5 mg-treated patient is not included
[3]One patient had two events of hand fracture

When corrected for pt-yrs of exposure, the incidence was still higher in saxagliptin (1.00 per 100 pt-yrs) versus comparator (0.6 per 100 pt-yrs). Only one fracture occurred in the setting of a MVA. Nonclinical studies have not identified an adverse effect of saxagliptin on bone morphology.

Although the number of fractures is low and a mechanistic basis to attribute these findings to saxagliptin is not evident, the labeling will still need to include these findings and the applicant should include a prospective assessment of bone fractures in its planned CV safety trial.

9. Advisory Committee Meeting

This NDA was presented before the Endocrine and Metabolic Advisory Committee on April 1, 2009. The basis for this public advisory committee meeting was to determine if data submitted with this NDA would satisfy the recent requirements for ruling out an unacceptable increase in CV risk with all new anti-diabetic therapies. The following 2 questions were posed to the panel members with the resulting votes following each question.

1. *Based on the preceding discussion, has the applicant provided appropriate evidence of cardiovascular safety to conclude that saxagliptin rules out an unacceptable excess cardiovascular risk relative to comparators, including evidence that the upper bound of the two-sided 95% confidence interval for the risk ratios/odds ratios is less than 1.8?*

Vote: 10 yes, 2 no Ten panel members voted yes and two panel members voted no.

2. For the Custom MACE endpoint, the upper bound of the two-sided 95% confidence interval for the risk ratios/odds ratio was less than 1.3. These data involved a total of 11 cardiovascular events in the 24-week double-blind short-term study periods and a total of 40 cardiovascular events in the combined short-term and long-term study periods of median 62-week exposure. Are these data adequate to conclude that post-marketing cardiovascular safety trials are unnecessary?

Vote: 0 yes, 12 no

Dr. Joffe has provided a clear and concise summary of the discussions surrounding these votes in his memo.

10. Pediatrics

Pediatric studies are waived for children between 0 and 9 years (inclusive) of age due to the low prevalence of type 2 diabetes in this age group. Pediatric studies for children from ages 10 to 16 years (inclusive) of age are being deferred. Under PREA, this is a required study and the applicant is expected to provide final study report for a randomized, controlled trial evaluating efficacy and safety of saxagliptin in approximately 140 pediatric patients with type 2 diabetes by June 30, 2015. The proposed pediatric plan has been discussed with the Pediatric Research Committee and is deemed acceptable.

11. Other Relevant Regulatory Issues

- A tradename review was conducted by and Onglyza® was deemed acceptable
- DSI conducted inspections of 4 clinical sties and HbA1c data were reviewed from two clinical laboratories. Minor violations were noted but the overall recommendation was NAI.
- Dr. Lowy has completed a review of financial disclosure documentations. Two investigators disclosed conflicts of financial interest; however, there were very few patients enrolled at these sites to contribute significantly to the overall database of > 4000 patients.

There are no other outstanding regulatory issues at this time.

12. Labeling

All labeling materials have been reviewed by different Offices and Divisions within the agency including, OND and OSE, and there are no outstanding issues precluding approval.

13. Decision/Action/Risk Benefit Assessment

- Regulatory Action

I am recommending the approval of this NDA.

- Risk Benefit Assessment

Saxagliptin is an effective glucose-lowering agent. However, when considering the degree of HbA1c reduction observed across the many classes of anti-diabetic therapies, it would appear that saxagliptin is a modest contributor as a glucose-lowering agent. This is by no means, a definitive assessment based on comparative efficacy studies, but more based on the data from this NDA which revealed a range of HbA1c reduction of 0.4-0.8% in a patient population whose Baseline HbA1c averaged 8.0. In the one study which enrolled patients with much worse glycemic control (Baseline HbA1c > 9.0), the efficacy of saxagliptin monotherapy was inferior to metformin monotherapy and combination therapy. Given these findings, saxagliptin monotherapy is not a reasonable initial strategy and under these circumstances, saxagliptin should be considered for add-on therapy. And in this respect, much of the labeling negotiations focused on describing efficacy such that the company is circumscribed in its promotional activities.

Despite the modest efficacy with saxagliptin, I would still conclude it has a role to play in the management of type 2 diabetes. First is the recognition that type 2 diabetes is a chronic and progressive disease in which the majority of patients will ultimately require multiple drugs to control hyperglycemia. In that vein, the applicant was able to demonstrate that the addition of saxagliptin to other available anti-diabetics (metformin, SUs, and TZDs) provided additional glucose-lowering that is deemed to be clinically relevant.

As any anti-diabetic therapy carries some undesirable side-effects unique to itself or its class of drug, the availability of several therapies which do not have overlapping side-effects provides important choices for clinicians to make in individualizing treatment. In this setting, saxagliptin provides an advantage in that a lower risk of hypoglycemia is expected over some other agents (e.g., sulfonylureas and insulin), it is not associated with weight gain (e.g., SUs, TZDs, and insulin), and it is not administered via injection (e.g., insulin, exenatide, pramlintide).

And finally, an important factor in approving this NDA is the CV safety profile that does not appear to suggest an excess risk. However, this preliminary assessment is based on studies which were not designed to prospectively adjudicate for CV events and had overall low CV

event rates. As such, a more definitive assessment will be necessary in a dedicated CV safety trial that can also be utilized for the assessment of other safety signals observed in this NDA and for the class of DPP4-inhibitors.

- Recommendation for Postmarketing Risk Evaluation and Mitigation Strategies

This NDA will not be approved with a REMS. However, selected postmarketing safety concerns have been discussed with OSE staff during the pre-approval safety conference and the applicant will highlight these safety concerns in their periodic safety updates.

- Recommendation for other Postmarketing Requirements and Commitments

The following are postmarketing required studies/trials incorporated into the action letter:

1. Pediatric clinical studies required under PREA
2. Two embryofetal development studies with saxagliptin + metformin to be conducted under FDAAA
3. An epidemiologic study to compare the risk of severe hepatic events among patients with T2DM exposed to saxagliptin vs other anti-diabetic therapies to be conducted under FDAAA
4. An epidemiologic study to compare severe hypersensitivity and severe cutaneous reactions among patients with T2DM exposed to saxagliptin versus other anti-diabetic therapies to be conducted under FDAAA
5. A dedicated CV safety trial with a primary objective of ruling out an excess CV risk of 1.3. This study will also have embedded in it other prospective assessments of safety concerns identified in this NDA and/or the class of DPP4 inhibitors. This trial is being conducted under FDAAA.

Linked Applications	Submission Type/Number	Sponsor Name	Drug Name / Subject
IDA 22350	ORIG 1	BRISTOL MYERS SQUIBB CO	SAXAGLIPTIN

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MARY H PARKS
07/29/2009